

- (17) BAIR, W.J. Inhalation of radionuclides and carcinogenesis. In: Hanna, M.G., Jr., Nettesheim, P., Gilbert, J.R. (Editors). *Inhalation Carcinogenesis*. Proceedings of a Biology Division, Oak Ridge National Laboratory Conference, Gatlinburg, Tennessee, October 8-11, 1969. U.S. Atomic Energy Commission Symposium Series 18, April 1970, pp. 77-101.
- (18) BEAMIS, J.F., Jr., STEIN, A., ANDREWS, J.L., Jr. Changing epidemiology of lung cancer. Increasing incidence in women. *Medical Clinics of North America* 59(2): 315-325, March 1975.
- (19) BELCHER, J.R. Adenocarcinoma and smoking. Communications to the Editor. *Chest* 67(5):622-623, May 1975.
- (20) BENNINGTON, J.L., FERGUSON, B.R., CAMPBELL, P.B. Epidemiologic studies of carcinoma of the kidney. II. Association of renal adenoma with smoking. *Cancer* 22(4): 821-823, October 1968.
- (21) BENNINGTON, J.L., LAUBSCHER, F.A. Epidemiologic studies on carcinoma of the kidney. I. Association of renal adenocarcinoma with smoking. *Cancer* 21(6): 1069-1071, June 1968.
- (22) BERNARDE, M.A., WEISS, W. A cohort analysis of pancreatic cancer, 1939-1969. *Cancer* 39(3): 1260-1263, March 1977.
- (23) BERNFELD, P., HOMBURGER, F., RUSSFELD, A.B. Strain differences in the response of inbred Syrian hamsters to cigarette smoke inhalation. *Journal of the National Cancer Institute* 53(4): 1141-1157, October 1974.
- (24) BERNFELD, P., HOMBURGER, F., SOTO, E., PAI, K.J. Cigarette smoke inhalation studies in inbred Syrian golden hamsters. *Journal of the National Cancer Institute* 63(3): 675-689, September 1979.
- (25) BERRY, G., NEWHOUSE, M.L., TUROK, M. Combined effect of asbestos exposure and smoking on mortality from lung cancer in factory workers. *Lancet* 2(7775): 476-479, September 2, 1972.
- (26) BEST, E.W.R. *A Canadian Study of Smoking and Health*. Ottawa, Department of National Health and Welfare, Epidemiology Division, Health Services Branch, Biostatistics Division, Research and Statistics Directorate, 1966, pp. 65-86.
- (27) BEST, E.W.R., JOSIE, G.H., WALKER, C.B. A Canadian study of mortality in relation to smoking habits: A preliminary report. *Canadian Journal of Public Health* 52: 99-106, March 1961.
- (28) BLACK, H., ACKERMAN, L.V. The importance of epidermoid carcinoma *in situ* in the histogenesis of carcinoma of the lung. *Annals of Surgery* 136(1): 44-55, July 1952.
- (29) BLOT, W.J., FRAUMENI, J.F., Jr. Geographic patterns of oral cancer in the United States: Etiologic implications. *Journal of Chronic Diseases* 30(11): 745-757, November 1977.
- (30) BLOT, W.J., MORRIS, L.E., STROUBE, R., TAGNON, I., FRAUMENI, J.F., Jr. Lung and laryngeal cancers in relation to shipyard employment in coastal Virginia. *Journal of the National Cancer Institute* 65(3): 571-575, September 1980.
- (31) BLUMLEIN, H. Zur kausalen Pathogenese des Larynxkarzinoms unter Berücksichtigung des Tabakrauchens. [Causal pathogenesis of laryngeal carcinoma with respect to tobacco smoking.] *Archiv für Hygiene und Bakteriologie München* 139: 349-404, 1955.
- (32) BORLAND, R., HARD, G.C. Early appearance of "transformed" cells from the kidneys of rats treated with a "single" carcinogenic dose of dimethylnitrosamine (DMN) detected by culture *in vitro*. *European Journal of Cancer* 10(3): 177-184, March 1974.
- (33) BRADSHAW, E., SCHONLAND, M. Oesophageal and lung cancers in Natal African males in relation to certain socio-economic factors. An analysis of 484 interviews. *British Journal of Cancer* 23(2): 275-284, June 1969.

- (34) BRESLOW, L., HOAGLIN, L., RASMUSSEN, G., ABRAMS, H.K. Occupations and cigarette smoking as factors in lung cancer. *American Journal of Public Health and the Nation's Health* 44(2): 171-181, February 1954.
- (35) BRIDGER, G.P., REAY-YOUNG, P. Laryngeal cancer and smoking. *Medical Journal of Australia* 2(8): 293-294, August 21, 1976.
- (36) BRODERS, A.C. Squamous-cell epithelioma of the lip. A study of five hundred and thirty-seven cases. *Journal of the American Medical Association* 74(10): 656-664, March 6, 1920.
- (37) BROWNE, R.M., CAMSEY, M.C., WATERHOUSE, J.A.H., MANNING, G.L. Etiological factors in oral squamous cell carcinoma. *Community Dentistry and Oral Epidemiology* 5: 301-306, 2977.
- (38) BUCKLEY, J.D., DOLL, R., HARRIS, R.W.C., VESSEY, M.P., WILLIAMS, P.T. Case control study of the husbands of women with dysplasia or carcinoma of the cervix uteri. *Lancet* 8254(II): 1010-1014, 1981.
- (39) CARNES, W.H. The respiratory epithelium of patients with lung cancer. In: *The Morphological Precursors of Cancer*. Proceedings of an International Conference held at the University of Perugia, Italy, June 26-30, 1961, pp. 625-634.
- (40) CARNOW, B.W. The "urban factor" and lung cancer: Cigarette smoking or air pollution? *Environmental Health Perspectives* 22: 17-21, February 1978.
- (41) CEDERLOF, R., DOLL, R., FOWLER, B., FRIBERG, L., NELSON, N., VOUK, V. (Editors). Air pollution and cancer: Risk assessment methodology and epidemiological evidence. Report of a task group. *Environmental Health Perspectives* 22: 1-12, February 1978.
- (42) CEDERLOF, R., FRIBERG, L., HRUBEC, Z., LORICH, U. *The Relationship of Smoking and Some Social Covariables to Mortality and Cancer Morbidity*. A ten year follow-up in a probability sample of 55,000 subjects, age 18-69, Part 1 and Part 2. Stockholm, Sweden, Department of Environmental Hygiene, The Karolinska Institute, 1975, pp. 1-91.
- (43) CEDERLOF, R., FRIBERG, L., LUNDMAN, T. The interactions of smoking, environment and heredity and their implications for disease etiology. A report of epidemiological studies on the Swedish Twin Registries. *Acta Medica Scandinavica*. Supplementum 612: 1-128, September 1977.
- (44) CHODYNICKI, S., GINDZIENSKA, E., TUPALSKA, M., HASSMANN, E. Epidemiological characteristics of patients with laryngeal cancer and precancerous conditions. *Otolaryngologia Polska* 34(4): 377-382, 1980.
- (45) CLAYSON, D.B. Occupational bladder cancer. *Preventive Medicine* 5(2): 228-244, June 1976. (Abstract)
- (46) COBB, B.G., ANSELL, J.S. Cigarette smoking and cancer of the bladder. *Journal of the American Medical Association* 193(5): 329-332, August 2, 1965.
- (47) COLE, P. Cancer and occupation: Status and needs of epidemiologic research. *Cancer* 39(40): 1788-1791, April 1977.
- (48) COLE, P., MONSON, R.R., HANING, H., FRIEDEL, G.H. Smoking and cancer of the lower urinary tract. *New England Journal of Medicine* 284(3): 129-134, January 21, 1971.
- (49) CORNFIELD, J. A method of estimating comparative rates from clinical data. Applications to cancer of the lung, breast, and cervix. *Journal of the National Cancer Institute* 11: 1269-1275, 1951.
- (50) CRONINGER, A.B., GRAHAM, E.A., WYNDER, E.L. Experimental production of carcinoma with tobacco products. V. Carcinoma induction in mice with cigar, pipe, and all-tobacco cigarette tar. *Cancer Research* 18(11): 1263-1271, December 1958.

- (51) CUNNINGHAM, G.J., WINSTANLEY, D.P. Hyperplasia and metaplasia in the bronchial epithelium. *Annals of the Royal College of Surgeons of England* 24(5): 323-330, May 1959.
- (52) DALY, C.J., STRONG, E.W. Carcinoma of the glottic larynx. *American Journal of Surgery* 130(4): 489-492, 1975.
- (53) DAVIES, R.F., DAY, T.D. A study of the comparative carcinogenicity of cigarette and cigar smoke condensate on mouse skin. *British Journal of Cancer* 23(2): 363-368, June 1969.
- (54) DEANER, R.M., TRUMMER, M.J. Carcinoma of the lung in women. *Journal of Thoracic and Cardiovascular Surgery* 59(4): 551-554, April 1970.
- (55) DEELEY, T.J., COHEN, S.L. The relationship between cancer of the bladder and smoking. In: *Bladder Cancer*. Proceedings of the 5th Inter-American Conference on Toxicology and Occupational Medicine, Coral Gables, Florida, University of Miami, School of Medicine, 1967, pp. 163-169.
- (56) DEVINE, K.D. Pathologic effects of smoking on the larynx and oral cavity. *Proceedings of the Mayo Clinic* 35(13): 349-352, June 22, 1960.
- (57) DOLL, R. Etiology of lung cancer. *Advances in Cancer Research* 3: 1-50, 1955.
- (58) DOLL, R. Strategy for detection of cancer hazards to man. *Nature* 265(5595): 589-596, February 17, 1977.
- (59) DOLL, R. Atmospheric pollution and lung cancer. *Environmental Health Perspectives* 22: 23-31, February 1978.
- (60) DOLL, R., GRAY, R., HAFNER, B., PETO, R. Mortality in relation to smoking: 22 years' observations on female British doctors. *British Medical Journal* 280(6219): 967-971, April 5, 1980.
- (61) DOLL, R., HILL, A.B. A study of the aetiology of carcinoma of the lung. *British Medical Journal* 2: 1271-1286, December 13, 1952.
- (62) DOLL, R., HILL, A.B. The mortality of doctors in relation to their smoking habits; a preliminary report. *British Medical Journal* 1(4877): 1451-1455, June 26, 1954.
- (63) DOLL, R., HILL, A.B. Lung cancer and other causes of death in relation to smoking. A second report on the mortality of British doctors. *British Medical Journal* 2: 1071-1081, 1956.
- (64) DOLL, R., HILL, A.B. Mortality in relation to smoking: Ten years' observations of British doctors (Part 1). *British Medical Journal* 1(5395): 1399-1410, May 30, 1964.
- (65) DOLL, R., HILL, A.B. Mortality in relation to smoking: Ten years' observations of British doctors. Concluded. *British Medical Journal* 1(5396): 1460-1467, June 6, 1964.
- (66) DOLL, R., HILL, A.B. Mortality of British doctors in relation to smoking: Observations on coronary thrombosis. In: Haenzel, W. (Editor). *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases*. National Cancer Institute Monograph No. 19. U.S. Department of Health, Education, and Welfare, Public Health Service, National Cancer Institute, January 1966, pp. 205-268.
- (67) DOLL, R., HILL, A.B., KREYBERG, L. The significance of cell type in relation to the aetiology of lung cancer. *British Journal of Cancer* II: 43-48, 1957.
- (68) DOLL, R., PETO, R. Mortality in relation to smoking: 20 years' observations on male British doctors. *British Medical Journal* 2(6051): 1525-1536, December 25, 1976.
- (69) DOLL, R., PETO, R. Mortality among doctors in different occupations. *British Medical Journal* 1(6074): 1433-1436, June 4, 1977.
- (70) DOLL, R., PETO, R. The causes of cancer: Quantitative estimates of avoidable risks of cancer in the United States today. *Journal of the National Cancer Institute* 66(6): 1191-1308, June 1981.

- (71) DOLL, R., PIKE, M.C. Trends in mortality among British doctors in relation to their smoking habits. *Journal of the Royal College of Physicians* 6(2): 216-222, January 1972.
- (72) DONTENWILL, W., CHEVALIER, H.-J., HARKE, H.-P., KLIMISCH, H.-J., KUHNIGK, C., RECKZEH, G., SCHNEIDER, B. Untersuchungen über den Effekt der chronischen Zigarettenrauchinhalation beim Syrischen Goldhamster und über die Bedeutung des Vitamin A auf die bei Berauchung gefundenen Organveränderungen. [Studies on the effect of chronic cigarette smoke inhalation in Syrian golden hamsters and the importance of Vitamin A on morphological alterations after smoke exposure.] *Zeitschrift für Krebsforschung und Klinische Onkologie* 89(2): 153-180, 1977.
- (73) DONTENWILL, W., CHEVALIER, H.-J., HARKE, H.-P., LAFRENZ, U., RECKZEH, G., SCHNEIDER, B. Investigations on the effects of chronic cigarette-smoke inhalation in Syrian golden hamsters. *Journal of the National Cancer Institute* 51(6):1781-1832, December 1973.
- (74) DORN, H.F. The mortality of smokers and nonsmokers. *Proceedings of the Social Statistics Section of the American Statistical Association*. Papers presented at the Annual Meeting of the American Statistical Association, Chicago, Illinois, December 27-30, 1958. Washington, D.C., American Statistical Association, 1959, pp. 34-71.
- (75) DUNHAM, L.J., RABSON, A.S., STEWART, H.L., FRANK, A.S., YOUNG, J.L., Jr. Rates, interview, and pathology study of cancer of the urinary bladder in New Orleans, Louisiana. *Journal of the National Cancer Institute* 41(3): 683-709, September 1968.
- (76) DUNN, J.E., LINDEN, G., BRESLOW, L. Lung cancer mortality experience of men in certain occupations in California. *American Journal of Public Health* 50(10): 1475-1487, October 1960.
- (77) DUTTA-CHOUDHURI, R., ROY, H., SEN GUPTA, B.K. Cancer of the larynx and hypopharynx. A clinicopathological study with special reference to aetiology. *Journal of the Indian Medical Association* 32(9): 352-362, May 1, 1959.
- (78) ENSTROM, J.E. Cancer mortality among low-risk population. *CA—A Cancer Journal for Clinicians* 29(6): 352-361, November-December 1979.
- (79) ENSTROM, J.E. Cancer mortality among Mormons in California during 1968-1975. *Journal of the National Cancer Institute* 65(5): 1073-1082, November 1980.
- (80) EVANS, A.S. 1976. Causation and disease: The Henle-Koch postulates revisited. *Yale Journal of Biology and Medicine* 49(2): 175-195, May 1976.
- (81) FEDERAL TRADE COMMISSION. *Report of "Tar," Nicotine and Carbon Monoxide of the Smoke of 200 Varieties of Cigarettes*. Washington, D.C., Federal Trade Commission, December 1981.
- (82) FISHER, R.A. Danger of cigarette smoking. *British Medical Journal* 2: 297-298, 1957. (Letter to the Editor).
- (83) FISHER, R.A. *Smoking, the Cancer Controversy. Some Attempts to Assess the Evidence*. Oliver and Boyd, Edinburgh, 1959, 47 pp.
- (84) FLAMM, H., KUNZE, M., KUNZE, M.J. *Tumoren der Harnblase und Zigarettenrauchen*. [Tumors of the urinary bladder and cigarette smoking.] Österreichisches Bundesinstitut für Gesundheitswesen, Vienna, 1975.
- (85) FLANDERS, W.D., ROTHMAN, K.J. Interaction of alcohol and tobacco in laryngeal cancer. *American Journal of Epidemiology*, in press.
- (86) GARFINKEL, L. Cancer mortality in nonsmokers: Prospective study by the American Cancer Society. *Journal of the National Cancer Institute* 65(5): 1169-1173, November 1980.

- (87) GELFAND, M., GRAHAM, A.J.P., LIGHTMAN, S. Carcinoma of bronchus and the smoking habit in Rhodesian Africans. *British Medical Journal* 3(5616): 468-469, August 24, 1968.
- (88) GRAHAM, S., DAYAL, H., ROHRER, T., SWANSON, M., SULTZ, H., SHEDD, D., FISCHMAN, S. Dentition, diet, tobacco, and alcohol in the epidemiology of oral cancer. *Journal of the National Cancer Institute* 59(6): 1611-1618, December 1977.
- (89) GRAY, S.H. CORDONNIER, J. Early carcinoma of the lung. A. M. A. *Archives of Surgery* 19: 1618-1626, 1929.
- (90) GSELL, O. Carcinome bronchique et tabac. [Bronchial carcinoma and tobacco.] *Medecine et Hygiene* 12(279): 429-431, December 1, 1954.
- (91) HAENSZEL, W., KURIHARA, M., LOCKE, F.B., SHIMUZU, K., SEGI, M. Stomach cancer in Japan. *Journal of the National Cancer Institute* 56(2): 265-274, February 1976.
- (92) HAENSZEL, W., KURIHARA, M., SEGI, M., LEE, R.K.C. Stomach cancer among Japanese in Hawaii. *Journal of the National Cancer Institute* 49: 969-988, 1972.
- (93) HAENSZEL, W., LOVELAND, D.B., SIRKEN, M.G. Lung-cancer mortality as related to residence and smoking histories. I. White males. *Journal of the National Cancer Institute* 28(4): 947-1001, April 1962.
- (94) HAENSZEL, W., SHIMKIN, M.B. A retrospective study of lung cancer in women. *Journal of the National Cancer Institute* 21(5): 825-842, November 1958.
- (95) HAENSZEL, W., TAEUBER, K.E. Lung-cancer mortality as related to residence and smoking histories. II. White females *Journal of the National Cancer Institute* 32(4): 803-838, April 1964.
- (96) HAMILTON, J.D., BROWN, T.C., MacDONALD, F.W. Morphological changes in smokers' lungs. *Canadian Medical Association Journal* 77(3): 177-182, August 1, 1957.
- (97) HAMMOND, E.C. Evidence on the effects of giving up cigarette smoking. *American Journal of Public Health* 55(5): 682-691, May 1965.
- (98) HAMMOND, E.C. Smoking in relation to the death rates of one million men and women. In: Haenszel, W. (Editor). *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases*. National Cancer Institute Monograph No. 19. U.S. Department of Health, Education, and Welfare, Public Health Service, National Cancer Institute, January 1966, pp. 127-204.
- (99) HAMMOND, E.C. Smoking habits and air pollution in relation to lung cancer. In: Lee, D.H.K. (Editor). *Environmental Factors in Respiratory Disease*. Fogarty International Center Proceedings No. 11, New York, Academic Press, 1972, pp. 177-198.
- (100) HAMMOND, E.C., GARFINKEL, L. Coronary heart disease, stroke, and aortic aneurysm. Factors in the etiology. *Archives of Environmental Health* 19(2): 167-182, August 1969.
- (101) HAMMOND, E.C., GARFINKEL, L. General air pollution and cancer in the United States. *Preventive Medicine* 9(2): 206-211, March 1980.
- (102) HAMMOND, E.C., GARFINKEL, L., SEIDMAN, H., LEW, E.A. "Tar" and nicotine content of cigarette smoke in relation to death rates. *Environmental Research* 12(3): 263-274, December 1976.
- (103) HAMMOND, E.C., GARFINKEL, L., SEIDMAN, H., LEW, E.A. Some recent findings concerning cigarette smoking. In: Hiatt, H.H., Watson, J.D., Winsten, J.A. (Editors). *Origins of Human Cancer. Book A: Incidence of Cancer in Humans*. Cold Spring Harbor Conference on Cell Proliferation, Volume 4. Cold Spring Harbor, New York, Cold Spring Harbor Laboratory, 1977, pp. 101-112.

- (104) HAMMOND, E.C., HORN, D. Smoking and death rates—Report on forty-four months of follow-up on 187,783 men. I. Total mortality. *Journal of the American Medical Association* 166(10): 1159–1172, March 8, 1958.
- (105) HAMMOND, E.C., HORN, D. Smoking and death rates—Report on forty-four months of follow-up of 187,783 men. II. Death rates by cause. *Journal of the American Medical Association* 166(11): 1294–1308, March 15, 1958.
- (106) HAMMOND, E.C., SEIDMAN, H. Smoking and cancer in the United States. *Preventive Medicine* 9(2): 169–173, March 1980.
- (107) HAMMOND, E.C., SELIKOFF, I.J. Relation of cigarette smoking to risk of death of asbestos-associated disease among insulation workers in the United States. In: Bogovski P., Gilson, J.C., Timbrell, V., Wagner, J.C., Davis, W. (Editors). *Biological Effects of Asbestos*. International Agency for Research on Cancer, Scientific Publication No. 8, Lyon, France, International Agency for Research on Cancer, 1973, pp. 312–317.
- (108) HARRIS, R.W.C., BRINTON, L.A., COWDELL, R.H., SKEGG, D.C.T., SMITH, P.G., VESSEY, M.P., DOLL, R. Characteristics of women with dysplasia or carcinoma *in situ* of the cervix uteri. *British Journal of Cancer* 42(359): 359–369, 1980.
- (109) HIGGINSON, J. Present trends in cancer epidemiology. In: Morgan, J.F. (Editor). *Proceedings of the Eighth Canadian Cancer Conference* Honey Harbour, Ontario, Canada, 1968. Elmsford, New York, Pergamon Press, 1969, pp. 43–75.
- (110) HIGGINSON, J. A hazardous society? Individual versus community responsibility in cancer prevention. *American Journal of Public Health* 66(4): 359–366, April 1976.
- (111) HIGGINSON, J., JENSEN, O.M. Epidemiological review of lung cancer in man. In: Mohr, E., Schmaehl, D., Tomatis, L. (Editors). *Air Pollution and Cancer in Man*. International Agency for Research on Cancer, Scientific Publication No. 16, Lyon, France, International Agency for Research on Cancer, 1977, pp. 169–189.
- (112) HILL, A.B. *The Environment and Disease: Association or Causation?* Proceedings of the Royal Society of Medicine, 58(5): 295–300, May 1965.
- (113) HINDS, M.W., KOLONEL, L.N., LEE, J., HIROHATA, T. Association between cancer incidence and alcohol/cigarette consumption among five ethnic groups in Hawaii. *British Journal of Cancer* 41(6): 929–940, June 1980.
- (114) HINDS, M.W., THOMAS, D.B., O'REILLY, H.P. Asbestos, dental x-rays, tobacco, and alcohol in the epidemiology of laryngeal cancer. *Cancer* 44(3): 1114–1120, September 1979.
- (115) HIRAYAMA, T. *Smoking in Relation to the Death Rates of 265,118 Men and Women in Japan*. Tokyo, National Cancer Center, Research Institute, Epidemiology Division, September 1967, 14 pp.
- (116) HIRAYAMA, T. Smoking and drinking—Is there a connection? *Smoke Signals* 16(7): 1–8, July 1970.
- (117) HIRAYAMA, T. *Smoking in Relation to the Death Rates of 265,118 Men and Women in Japan. A Report on 5 Years of Follow-up*. Presented at the American Cancer Society's 14th Science Writers' Seminar, Clearwater Beach, Florida, March 24–29, 1972, 15 pp.
- (118) HIRAYAMA, T. Operational aspects of cancer public education in Japan. In: *Summary Proceedings of the International Conference on Public Education About Cancer*. UICC Technical Report Series, Volume 18, Geneva, 1975, pp. 85–90.

- (119) HIRAYAMA, T. Prospective studies on cancer epidemiology based on census population in Japan. In: Bucalossi, P., Veronesi, U., Cascinelli, N. (Editors). *Cancer Epidemiology, Environmental Factors*. Volume 3. Proceedings of the 11th International Cancer Congress, Florence, Italy, October 20–26, 1974. Amsterdam, Excerpta Medica, 1975, pp. 26–35.
- (120) HIRAYAMA, T. Changing patterns of cancer in Japan with special reference to the decrease in stomach cancer mortality. In: Hiatt, H.H., Watson, J.D., Winsten, J.A. (Editors). *Origins of Human Cancer. Book A: Incidence of Cancer in Humans*. Cold Spring Harbor Conference on Cell Proliferation, Volume 4. Cold Spring Harbor, New York, Cold Spring Harbor Laboratory, 1977, pp. 55–75.
- (121) HITOSUGI, M. Epidemiological study of lung cancer with special reference to the effect of air pollution and smoking habit. *Bulletin of the Institute of Public Health* 17(3): 237–256, September 1968.
- (122) HOEY, J., MONTOERNAY, C., LAMBERT, R. Wine and tobacco: Risk factors for gastric cancer in France. *American Journal of Epidemiology* 113(6): 668–674, June 1981.
- (123) HOFFMANN, D., WYNDER, E.L. Environmental respiratory carcinogenesis. In: Searle, C.E. (Editor). *Chemical Carcinogens*. American Chemical Society Monograph 173. Washington, D.C., American Chemical Society, 1970, 324–365 pp.
- (124) HOLLAND, J.F., FREI, E. III. *Cancer Medicine*. Lea and Febiger, Philadelphia, 1974, pp. 1438, 1797.
- (125) HOMBURGER, F. "Smokers' Larynx" and carcinoma of the larynx in Syrian hamsters exposed to cigarette smoke. *Laryngoscope* 85(11, Part 1): 1874–1881, November, 1975.
- (126) HOMBURGER, F., SOTO, H., ALTHOFF, J., DALQUEN, P., HEITZ, P. Carcinoma of the larynx in hamsters exposed to cigarette smoke. *American Journal of Pathology* 95: 845–848, June 1979.
- (127) HOMBURGER, F., TREGER, A., BAKER, J.R. Mouse-skin painting with smoke condensates from cigarettes made of pipe, cigar, and cigarette tobacco. *Journal of the National Cancer Institute* 31(6): 1445–1459, December 1963.
- (128) HOOVER, R., COLE, P. Population trends in cigarette smoking and bladder cancer. *American Journal of Epidemiology* 94(5): 409–418, November 1971.
- (129) HOWE, G.R., BURCH, J.D., MILLER, A.B., COOK, G.M., ESTEVE, J., MORRISON, B., GORDON, P., CHAMBERS, L.W., FODOR, G., WINSOR, G.M. Tobacco use, occupation, coffee, various nutrients, and bladder cancer. *Journal of the National Cancer Institute* 64(4):701–713, April 1980.
- (130) JASMIN, G., CHA, J.W. Renal adenomas induced in rats by dimethylnitrosamine. An electron microscopic study. *Archives of Pathology* 87(3): 267, March 1969.
- (131) KAHN, H.A. The Dorn study of smoking and mortality among U.S. veterans: Report on eight and one-half years of observation. In: Haenszel, W. (Editor). *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases*. National Cancer Institute Monograph No. 19, U.S. Department of Health, Education, and Welfare, Public Health Service, National Cancer Institute, January 1966, pp. 1–125.
- (132) KAMIONKOWSKI, M.D., FLESHLER, B. The role of alcoholic intake in esophageal carcinoma. *American Journal of the Medical Sciences* 249(6): 696–700, June 1965.

- (133) KARBE, E., KOSTER, K. Carcinogenicity of inhaled cigarette smoke in the NMU-pretreated hamster larynx. In: Karbe, E., Park, J.F. (Editors). *Experimental Lung Cancer: Carcinogenesis and Bioassays*. International Symposium, Seattle, Washington, June 23-26, 1974. New York, Springer-Verlag, 1974, pp. 369-382.
- (134) KASPERSKI, A. Occurrence of laryngeal carcinoma in Bydgoszcz County (1955-75) with regard to some epidemiological factors. *Otolaryngologia Polska* 34(1): 125-126, 1980.
- (135) KELLER, A.Z. Cirrhosis of the liver, alcoholism and heavy smoking associated with cancer of the mouth and pharynx. *Cancer* 20(6): 1015-1022, June 1967.
- (136) KELLER, A.Z., TERRIS, M. The association of alcohol and tobacco with cancer of the mouth and pharynx. *American Journal of Public Health* 55(10): 1578-1585, October 1965.
- (137) KENNEDY, A. Relationship between cigarette smoking and histological type of lung cancer in women. *Thorax* 28(2): 204-208, March 1973.
- (138) KENSLER, C.J. The pharmacology of tobacco smoke effects of chronic exposure. In: James, G., Rosenthal, T. (Editors). *Tobacco and Health*. Springfield, Illinois, Charles C. Thomas, 1962, pp. 5-20.
- (139) KERR, W.K., BARKIN, M., LEVERS, P.E., WOO, S.K.-C., MENCZYK, Z. The effect of cigarette smoking on bladder carcinogens in man. *Canadian Medical Association Journal* 93(1): 1-7, July 3, 1965.
- (140) KESSLER, I.I., KULCAR, Z., ZIMOLO, A., GRGUREVIC, M. STRNAD, M., GOODWIN, B.J. Cervical cancer in Yugoslavia. II. Epidemiologic factors of possible etiologic significance. *Journal of the National Cancer Institute* 53(1): 51-60, July 1974.
- (141) KIDA, H., OMOTO, T., SAKAMOTO, K. MOMOSE, S. Fukuoka ken hokubu ni okeru boko shuyo no ekigaku to tokei. [Statistical and epidemiological studies on tumor of the urinary bladder in the northern parts of Fukuoka Prefecture.] *Hifu to Hinyo* 30(5): 883-889, October 1968.
- (142) KIRIKAE, I. Epidemiology of cancer of the larynx. *Japanese Journal of Clinical Medicine* 26(8): 1808-1811, August 1968.
- (143) KISSIN, B., KALEY, M.M., SU, W.H., LERNER, R. Head and neck cancer in alcoholics. The relationship to drinking, smoking, and dietary patterns. *Journal of the American Medical Association* 224(8): 1174-1175, May 21, 1973.
- (144) KNUDTSON, K.P. The pathologic effects of smoking tobacco on the trachea and bronchial mucosa. *American Journal of Clinical Pathology* 33(4): 310-317, April 1960.
- (145) KONTUREK, S.J., DALE, J., JACOBSON, E.D., JOHNSON, L.R. Mechanisms of nicotine-induced inhibition of pancreatic secretion of bicarbonate in the dog. *Gastroenterology* 62(3): 425-429, March 1972.
- (146) KOTIN, P., FALK, H.L. Polluted urban air and related environmental factors in the pathogenesis of pulmonary cancer. *Diseases of the Chest* 45(3): 236-246, March 1964.
- (147) KOULUMIES, M. Smoking and pulmonary carcinoma. *Acta Radiologica* 39: 255-260, 1953.
- (148) KREYBERG, L. Histological lung cancer types: A morphological and biological correlation. *Acta pathologica et Microbiologica Scandinavica*. (Supplementum 152), 1962, 92 pp.
- (149) KUNZE, M., VUTUC, C. Threshold of tar exposure: Analysis of smoking history of male lung cancer cases and controls. In: Gori, G.B., Bock, F.G. (Editors). *Banbury Report 3—A safe cigarette?* Cold Spring Harbor, New York, Cold Spring Harbor Laboratory, March 12, 1980, pp. 29-36.

- (150) KURATSUNE, M., KOHCHI, S., HORIE, A. Carcinogenesis in the esophagus. I. Penetration of benzo(a)pyrene and other hydrocarbons into the esophageal mucosa. *Gann* 56(2): 177-187, April 1965.
- (151) KURITA, H. Clinico-epidemiological study of stomach cancer considering sex and age differences. *Japan Journal of Cancer Clinics* 20(8): 580-593, 1974.
- (152) LANCASTER, H.O. Cancer statistics in Australia. Part II. Respiratory system. *Medical Journal of Australia* 1: 1006-1011, June 30, 1962.
- (153) LEE, B.K., MURPHY, G. Determination of arsenic content of American cigarettes by neutron activation analysis. *Cancer* 23(6): 1315-1317, June 1969.
- (154) LEE, P.N. (Editor). *Tobacco Consumption in Various Countries*. Research Paper No. 6, 4th Edition. London, Tobacco Research Council, 1975, 86 pp.
- (155) LEE, P.N., GARFINKEL, L. Mortality and type of cigarette smoked. *Journal of Epidemiology and Community Health* 35(1): 16-22, March 1981.
- (155a) LEVIN, M.L., GOLDSTEIN, H., GERHARDT, P.R. Cancer and tobacco smoking. A preliminary report. *Journal of the American Medical Association* 143(4): 336-338, May 27, 1950.
- (156) LICKINT, F. Der Tabakrauch als Ursache des Lungenkrebses. Spezieller Teil IV. Aetiologie und Prophylaxe des Lungenkrebses. [Tobacco smoke as cause of lung cancer. Special Section IV. In: *Etiology and Prophylaxis of Lung Cancer*.] Dresden, Theodor Steinkopff, 1953, pp. 76-102.
- (157) LILIENTHAL, A.M., LEVIN, M.L., MOORE, G.E. The association of smoking with cancer of the urinary bladder in humans. *American Medical Association Archives of Internal Medicine* 98: 129-135, 1956.
- (158) LILIENTHAL, A.M., LILIENTHAL, D.E. *Foundations of Epidemiology*. 2nd Edition, New York, Oxford University Press, 1980.
- (159) LOCKWOOD, K. On the etiology of bladder tumors in Kobenhavn-Frederiksberg. An inquiry of 369 patients and 369 controls. *Acta Pathologica et Microbiologica Scandinavica* 51(Supplementum 145): 1-166, 1961.
- (160) LOMBARD, H.L., DOERING, C.R. Classics in oncology. Cancer studies in Massachusetts. 2. Habits, characteristics and environment of individuals with and without cancer. *New England Journal of Medicine* 198: 481-487, 1928.
- (161) LOMBARD, H.L., SNEGIREFF, L.S. An epidemiological study of lung cancer. *Cancer* 12(2): 406-413, March-April 1959.
- (162) LONGNECKER, D.S., SHINOZUKA, H., DEKKER, A. Focal acinar cell dysplasia in human pancreas. *Cancer* 45(3): 534-540, February 1, 1980.
- (163) LUNDIN, F.E., Jr., LLOYD, J.W., SMITH, E.M., ARCHER, V.E., HOLADAY, D.A. Mortality of uranium miners in relation to radiation exposure, hard-rock mining and cigarette smoking—1950 through September 1967. *Health Physics* 16(5): 571-578, May 1969.
- (164) LYON, J.L., GARDNER, J.W., WEST, D.W. Cancer in Utah: Risk by religion and place of residence. *Journal of the National Cancer Institute* 65(5): 1063-1071, November 1980.
- (165) LYON, J.L., GARDNER, J.W., WEST, D.W. Cancer incidence in Mormons and Non-Mormons in Utah during 1967-1975. *Journal of the National Cancer Institute* 65(5): 1055-1061, November 1980.
- (166) LYON, J.L., GARDNER, J.W., WEST, D.W. Cancer risk and life-style: Cancer among Mormons from 1967-1975. In: Cairns, J., Lyon, J.L., Skolnick, M. (Editors). *Cancer Incidence in Defined Populations*. Banbury Report No. 4, Cold Spring Harbor, New York, Cold Spring Harbor Laboratory, 1980, pp. 3-30.

- (167) MacDONALD, I.G. Statement of Ian G. MacDonald, University of Southern California. In: *Hearings Before the Legal and Monetary Subcommittee of the Committee on Government Operations: False and Misleading Advertising (Filter-Tip Cigarettes)*. July 18, 19, 23-26, 1957, U.S. House of Representatives. Government Printing Office, 1957, pp. 34-61.
- (168) MacMAHON, B., PUGH, T. *Epidemiology: Principles, and Methods*. Boston, Little Brown and Company, 1970, pp. 17-27.
- (169) MacMAHON, B., YEN, S, TRICHOPOULOS, D., WARREN, K., NARDI, G. Coffee and cancer of the pancreas. *New England Journal of Medicine* 304(11): 630-633, 1981.
- (170) MAKHYOUN, N.A. Smoking and bladder cancer in Egypt. *British Journal of Cancer* 30(6): 577-581, December 1974.
- (171) MALTONI, C., CARRETTI, D., CANEPARI, C., GHETTI, G. Incidenza della metaplasia squamosa dell'epitelio respiratorio in rapporto al fumo di sigaretta. Studio citologico su 1000 individui di sesso maschile apparentemente sani. [Incidence of squamous metaplasia of the respiratory epithelium in relation to cigarette smoking. Cytological study on 1000 apparently healthy male individuals.] *Cancro* 21(4): 349-356, 1968.
- (172) MARTINEZ, I. Factors associated with cancer of the esophagus, mouth and pharynx in Puerto Rico. *Journal of the National Cancer Institute* 42(6): 1069-1094, June 1969.
- (173) MARTINEZ, I. Retrospective and prospective study of carcinoma of the esophagus, mouth, and pharynx in Puerto Rico. *Boletin de la Asociacion Medica de Puerto Rico* 62(6): 170-178, June 1970.
- (174) MARTISCHNIG, K.M., NEWELL, D.J., BARNSLEY, W.C., COWAN, W.K., FEINMANN, E.L., OLIVER, E. Unsuspected exposure to asbestos and bronchogenic carcinoma. *British Medical Journal* 1(6063): 746-749, March 19, 1977.
- (175) MASON, T.J., McKAY, F.W., HOOVER, R., BLOT, W.J., FRAUMENI, J.F. *Atlas of Cancer Mortality for U.S. Counties. 1950-1969*. Washington, D.C., Government Printing Office, DHEW Publication No. (NIH)75-780, 1975.
- (176) MATTHEWS, M.J., GORDON, P.R. Morphology of pulmonary and pleural malignancies. In: Straus, M.J. (Editor). *Lung Cancer Diagnosis and Treatment*. New York, Grune and Stratton, 1977.
- (177) MAXWELL, J.C., Jr. Trends in cigarette consumption. In: Gori, G.B., Bock, F.G. (Editors). *Banbury Report 3—A Safe Cigarette?* Cold Spring Harbor, New York, Cold Spring Harbor Laboratory, March 12, 1980, pp. 325-332.
- (178) McCONNELL, R.B., GORDON, K.C.T., JONES, T. Occupational and personal factors in the aetiology of carcinoma of the lung. *Lancet* 2: 651-656, October 4, 1952.
- (179) McLOY, D.G., HECHT, S.S., WYNDER, E.L. The roles of tobacco, alcohol, and diet in the etiology of upper alimentary and respiratory tract cancers. *Preventive Medicine* 9(5): 622-629, September 1980.
- (180) MEHTA, F.S., PINDBORG, J.J., BHONSLE, R.B., SINOR, P.N. Incidence of oral leucoplakias among 20,358 Indian villagers in a 7-year period. *British Journal of Cancer* 33(5): 549-554, May 1976.
- (181) MILLS, C.A., PORTER, M.M. Tobacco smoking habits and cancer of the mouth and respiratory system. *Cancer Research* 10: 539-542, 1950.
- (182) MILLS, C.A., PORTER, M.M. Tobacco smoking, motor exhaust fumes, and general air pollution in relation to lung cancer incidence. *Cancer Research* 17: 981-990, 1957.
- (183) MONSON, R.R., LYONS, J.L. Proportional mortality among alcoholics. *Cancer* 36(3): 1077-1079, September 1975.

- (184) MONTESANO, R., SAFFIOTTI, U., SHUBIK, P. The role of topical and systemic factors in experimental respiratory carcinogenesis. In: Hanna, M.G., Jr., Nettesheim, P., Gilbert, J.R. (Editors). *Inhalation Carcinogenesis*. Proceedings of a Biology Division, Oak Ridge National Laboratory Conference, Gatlinburg, Tennessee, October 8-11, 1969. Atomic Energy Commission, Division of Technical Information, AEC Symposium Series No. 18, April 1970, pp. 353-371.
- (185) MOOLGAVKAR, S.H., STEVENS, R.G. Smoking and cancers of bladder and pancreas: Risk and temporal trends. *Journal of the National Cancer Institute* 67(1): 15-23, July 1981.
- (186) MOORE, G.E., BISSINGER, L.L., PROEHL, E.C. Intraoral cancer and the use of chewing tobacco. *Journal of the American Geriatrics Society* 1: 497-506, 1953.
- (187) MORGAN, R.G.H., WORMSLEY, K.G. Progress report: Cancer of the pancreas. *Gut* 18(7): 580-596, July 1977.
- (188) MORGAN, R.W., JAIN, M.G. Bladder cancer—Smoking, beverages and artificial sweeteners. *Canadian Medical Association Journal* III(10): 1067-1070, November 16, 1974.
- (189) MOROSCO, G.J., GOORINGER, G.C. Lifestyle factors and cancer of the pancreas: A hypothetical mechanism. *Medical Hypothesis* 6(9): 971-985, September 1980.
- (190) MUELLER, K.M., KROHN, B.R. Smoking habits and their relationship to precancerous lesions of the larynx. *Journal of Cancer Research and Clinical Oncology* 96(2): 211-217, 1980.
- (191) MULLER, F.H. Tabakmissbrauch und Lungencarcinom. [Tobacco abuse and carcinoma of the lung.] *Zeitschrift für Krebsforschung* 49(1): 57-84, June 1939.
- (192) NAGUIB, S.M., LUNDIN, F.E., Jr., DAVID, H.J. Relation of various epidemiologic factors to cervical cancer as determined by a screening program. *Obstetrics and Gynecology* 28(4): 451-459, October 1966.
- (193) NASIELL, M. *The Epithelial Picture in the Bronchial Mucosa in Chronic Inflammatory and Neoplastic Lung Disease and its Relation to Smoking. A Comparative Histologic and Sputum-cytologic Study*. Stockholm, Cytology Laboratory, Department of Pathology at Sabbatsberg Hospital, Karolinska Institutet, 1968, 72 pp.
- (194) NATIONAL CANCER INSTITUTE. *End Results in Cancer*. Report No. 4., U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute. DHEW Publication No. (NIH)73-272, 1972, pp. 43-46, 81-84.
- (195) NATIONAL CANCER INSTITUTE. *Cancer Patient Survival*. Report No. 5, U.S. Department of Health Education and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute. DHEW Publication No. (NIH)77-922, 1976, pp. 11-55.
- (196) NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES, NATIONAL INSTITUTE FOR OCCUPATION SAFETY AND HEALTH. *Estimates of the Fraction of Cancer in the United States Related to Occupational Factors*. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, September 15, 1978, pp. 1-50.
- (197) NATIONAL CANCER INSTITUTE. *Surveillance Epidemiology End Results*. Incidence and mortality data: 1973-1977. National Cancer Institute Monograph No.57, U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Cancer Institute, 1981, 1082 pp.

- (198) NATIONAL CANCER INSTITUTE. Cancer Mortality in the United States, 1950-1977. In: McKay, F.W., Hanson, M.R., Miller, R.W. (Authors). *Journal of the National Cancer Institute*. Monograph No. 59, April 1982, 475 pp.
- (199) NATIONAL CENTER FOR HEALTH STATISTICS. Provisional statistics. Annual survey for the United States, 1980. *Monthly Vital Statistics Report*. Volume 29, No. 13, DHHS Publication No. (PHS)81-1120, September 17, 1981.
- (200) NATIONAL CENTER FOR HEALTH STATISTICS. *Mortality From Diseases Associated With Smoking: United States 1960-77*. Vital and Health Statistics, Series 20, No. 17, DHHS Publication No. (PHS)81-1854, 1981, 71 pp.
- (201) NEWMAN, G. Early diagnosis of cancer of the cervix—the detection of high-risk patients. *Geburtshilfe und Frauenheilkunde* 32(7): 564-568, July 1972.
- (202) NOVAK, J., HYBASEK, I., PELLANT, A. Cancer of the larynx. An epidemiological study of patients treated during the years 1946-1975 at the Oral Clinic in Hradec Kralove. *Cesk Otolaryngol* 26(3): 129-136, 1977.
- (203) OCHSNER, A., DEBAKEY, M. Primary pulmonary malignancy. Treatment by total pneumonectomy. Analysis of 79 collected cases and presentation of 7 personal cases. *Surgery, Gynecology and Obstetrics* 68: 435-451, 1939.
- (204) OLEARCHYK, A.S. Gastric carcinoma: A critical review of 243 cases. *American Journal of Gastroenterology* 70(1): 25-45, July 1978.
- (205) ORMOS, J., KARACSONYI, G., BILICZKI, F., SZONYI, F. Lung cancer in the Hungarian plain. *Neoplasma* 16(6): 667-675, 1969.
- (206) PAPANICOLAOU, G.N., KOPROWSKA, I. Carcinoma-in-situ of the right lower bronchus: A case report. *Cancer* 4(1): 141-146, January 1951.
- (207) PEACOCK, E.E., Jr., GREENBERG, B.G., BRAWLEY, B.W. The effect of snuff and tobacco on the production of oral carcinoma: An experimental and epidemiological study. *Annals of Surgery* 151: 542-550, 1960.
- (208) PELL, S., D'ALONZO, C.A. A five-year mortality study of alcoholics. *Journal of Occupational Medicine* 15(2): 120-125, February 1973.
- (209) PERNU, J. An epidemiological study on cancer of the digestive organs and respiratory system. A study based on 7,078 cases. *Annales Medicinæ Internæ Fenniae* 49(Supplement 33): 1-117, 1960.
- (210) PETO, R., SCHNEIDERMAN, M. *Quantification of Occupational Cancer*. Banbury Report No. 9, Cold Spring Harbor, New York, Cold Spring Harbor Laboratory, 1981, 756 pp.
- (211) PHILLIPS, R.L., KUZMA, J.W., LOTZ, T.M. Cancer mortality among comparable members versus nonmembers of the Seventh-Day Adventist Church. In: Cairns, J., Lyon, J.L., Skolnick, M. (Editors). *Cancer Incidence in Defined Populations*. Banbury Report No. 4, Cold Spring Harbor, New York, Cold Spring Harbor Laboratory, 1980, pp. 93-108.
- (212) PIKE, M.C., JING, J.S., RASHRIO, I.P., HENDERSON, B.E., MENCK, H.R. Occupation: "Explanation" of an apparent air pollution related localized excess of lung cancer in Los Angeles County. In: Whittemore, A.S., Breslow, N.E. (Editors). *Energy and Health*. Philadelphia Society for Industrial and Applied Mathematics, 1979, pp. 3-15.
- (213) POTTER, E.A., TULLY, M.R. The statistical approach to the cancer problem in Massachusetts. *American Journal of Public Health and the Nation's Health* 35(5): 485-490, May 1945.
- (214) POUND, A.W., LAWSON, T.A., HORN, L. Increased carcinogenic action of dimethylnitrosamine after prior administration of carbon tetrachloride. *British Journal of Cancer* 27(6): 451-459, June 1973.
- (215) RANDIG, K. Untersuchungen zur Atiologie des Bronchialkarzinoms. [Investigations on the etiology of bronchial carcinoma.] *Öffentliche Gesundheitsdienst* 16(9): 305-313, December 1954.

- (216) REIF, A.E. Public information on smoking: An urgent responsibility for cancer research workers. *Aspects of Cancer Research 1971-1978: Editorials from the Journal of the National Cancer Institute*. National Cancer Institute Monograph No. 52. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH)79-1863, September 1979, pp. 123-128.
- (217) REINGOLD, I.M., OTTOMAN, R.E., KONWALER, B.E. Bronchogenic carcinoma: A study of 60 necropsies. *American Journal of Clinical Pathology* 20: 515-525, 1950.
- (218) RICE, D.P., HODGSON, T.A. *Social and Economic Implications of Cancer in the United States*. U.S. Department of Health, Education, and Welfare, Public Health Service, National Center for Health Statistics, 1978, 82 pp.
- (219) RIMINGTON, J. The effect of filters on the incidence of lung cancer in cigarette smokers. *Environmental Research* 24(1): 162-166, February 1981.
- (220) ROBBINS, W.T. Bronchial epithelium in cigarette-smoking college students. *Journal of the American College Health Association* 20(3): 209-211, February 1972.
- (221) ROE, F.J.C., CLACK, J.C., BISHOP, D., PETO, R. Comparative carcinogenicity for mouse-skin of smoke condensates prepared from cigarettes made from the same tobacco cured by two processes. *British Journal of Cancer* 24(1): 107-121, March 1970.
- (222) ROGOT, E. *Smoking and General Mortality Among U.S. Veterans, 1954-1969*. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Heart and Lung Institute, Epidemiology Branch, DHEW Publication No. (NIH)74-544, 1974, 65 pp.
- (223) ROGOT, E. Smoking and mortality among U.S. veterans. *Journal of Chronic Diseases* 27: 189-203, 1974.
- (224) ROGOT, E., MURRAY, J.L. Smoking and causes of death among U.S. veterans: 16 years of observation. *Public Health Reports* 95(3): 213-222, May-June 1980.
- (225) ROSENOW, E.C., CARR, D.T. Bronchogenic carcinoma. CA—A *Cancer Journal for Clinicians* 29(4): 233-245, July-August 1979.
- (226) ROTHMAN, K.J. Alcohol. In: Fraumeni, J.F., Jr. (Editor). *Persons at High Risk of Cancer. An Approach to Cancer Etiology and Control*. New York, Academic Press, 1975, pp. 139-150.
- (227) ROTHMAN, K.J., KELLER, A. The effect of joint exposure to alcohol and tobacco on risk of cancer of the mouth and pharynx. *Journal of Chronic Diseases* 25: 711-716, 1972.
- (228) RYAN, R.F., McDONALD, J.R., DEVINE, K.D. The pathologic effects of smoking on the larynx. *Archives of Pathology* 60(5): 472-480, November 1955.
- (229) SACCOMANNO, G. Radiation exposure of uranium miners. *Hearings Before the Subcommittee on Research, Development, and Radiation of the Joint Committee on Atomic Energy: Radiation Standards for Uranium Mining*. Congress of the United States, 91st Congress, 1st Session, March 17 and 18, 1969, pp. 301-315.
- (230) SADOWSKY, D.A., GILLIAM, A.G., CORNFIELD, J. The statistical association between smoking and carcinoma of the lung. *Journal of the National Cancer Institute* 13(5): 1237-1258, April 1953.

- (231) SAFFIOTTI, U. Experimental respiratory tract carcinogenesis and its relation to inhalation exposures. In: Hanna, M.G., Jr., Nettesheim, P., Gilbert, J.R. (Editors). *Inhalation Carcinogenesis*. Proceedings of a Biology Division, Oak Ridge National Laboratory Conference, Gatlinburg, Tennessee, October 8-11. 1969. Atomic Energy Commission, Division of Technical Information EDC Symposium Series No. 18, April 1970, pp. 27-54.
- (232) SAFFIOTTI, U., CEFIS, F., KOLB, L.H. A method for the experimental induction of bronchogenic carcinoma. *Cancer Research* 28(1): 104-124, January 1968.
- (233) SANDERUD, K. Squamous metaplasia of the respiratory tract epithelium: An autopsy study of 214 cases. II. Relation to tobacco smoking, occupation and residence. *Acta Pathologica et Microbiologica Scandinavica* 43: 47-61, 1968.
- (234) SANGHVI, L.D., RAO, K.C.M., KHANOLKAR, V.R. Smoking and chewing of tobacco in relation to cancer of the upper alimentary tract. *British Medical Journal* 1: 1111-1114, 1955.
- (235) SATTERLEE, H.S. The problem of arsenic in American cigarette tobacco. *New England Journal of Medicine* 254(25): 1149-1156, 1956.
- (236) SCHAER, M., MUGGLER, J. Etiological differences between stomach cancer and cancer of the colon. *Sozial- und Praventivmedizin* 19(4): 245-250, July-August 1974.
- (237) SCHAIRER, E., SCHOENIGER, E. Lungenkrebs und Tabakverbrauch. [Lung cancer and tobacco use.] *Zeitschrift für Krebsforschung* 54: 261-269, 1943.
- (238) SCHMAUZ, R., COLE, P. Epidemiology of cancer of the renal pelvis and ureter. *Journal of the National Cancer Institute* 52(5): 1431-1434, May 1974.
- (239) SCHMIDT, W., De LINT, J. Causes of death of alcoholics. *Quarterly Journal of Studies on Alcohol* 33(1): 171-185, March 1972.
- (240) SCHNEIDERMAN, M.A. Time trends: United States 1953-1973. *Laryngoscope* 88(1, Supplement 8): 6, 44-49, 1978.
- (241) SCHOENBERG, B.S., BAILAR, J.C. III, FRAUMENI, J.F., Jr. Certain mortality patterns of esophageal cancer in the United States, 1930-1967. *Journal of the National Cancer Institute* 46(1): 63-73, January 1971.
- (242) SCHOTTENFELD, D. Alcohol as a co-factor in the etiology of cancer. *Cancer* 43(5, Supplement): 1962-1966, May 1979.
- (243) SCHOTTENFELD, D., GANTT, R.C., WYNDER, E.L. The role of alcohol and tobacco in multiple primary cancers of the upper digestive system, larynx, and lung: A prospective study. *Preventive Medicine* 3(2): 277-293, June 1974.
- (244) SCHREK, R., BAKER, A., BALLARD, G.P., DOLGOFF, S. Tobacco smoking as an etiologic factor in disease. I. Cancer. *Cancer Research* 10: 49-58, 1950.
- (245) SCHWARTZ, D., DENOIX, P.-F. L'enquete française sur l'etiologie du cancer broncho-pulmonaire. Role du tabac. [French investigation on the etiology of bronchopulmonary cancer. Role of tobacco.] *Semaine des Hopitaux de Paris* 33(62/7): 3630-3645, October 30, 1957.
- (246) SCHWARTZ, D., DENOIX, P.-F., ANGUERA, G. Recherche des localisations du cancer associees aux facteurs tabac et alcool chez l'homme. [Research on the localizations of cancer associated with tobacco and alcoholic factors in man.] *Bulletin de l'Association Francaise pour l'Etude du Cancer* 44: 336-361, 1957.
- (247) SCHWARTZ, D., FLAMANT, R., LELLOUCH, J., DENOIX, P.-F. Results of a French survey on the role of tobacco, particularly inhalation, in different cancer sites. *Journal of the National Cancer Institute* 26(5): 1085-1108, May 1961.

- (248) SEGI, M., FUKUSHIMA, I., FUJISAKU, S., KURIHARA, M., SAITO, S., ASANO, K., KAMOI, M. An epidemiological study on cancer in Japan. The report of the Committee for Epidemiological Study on Cancer, sponsored by the Ministry of Welfare and Public Health. *Gann* 48(Supplement): April 1957, 63 pp.
- (249) SELIKOFF, I.J., BADER, R.A., BADER, M.E., CHURG, J., HAMMOND, E.C. Asbestosis and neoplasia. *American Journal of Medicine* 42(4): 487-496, April 1967.
- (250) SELIKOFF, I.J., HAMMOND, E.C., CHURG, J.: Asbestos exposure, smoking, and neoplasia. *Journal of the American Medical Association* 204(2): 104-110, April 8, 1968.
- (251) SIMON, D., YEN, S., COLE, P. Coffee drinking and cancer of the lower urinary tract. *Journal of the National Cancer Institute* 54(3): 587-591, March 1975.
- (252) STASZEWSKI, J. Palenie a rak wargi, jamy ustnej, migdalkow i krtani. [Tobacco smoking and its relation to cancer of the mouth, tonsils and larynx.] *Nowotwory* 10(2): 121-132, 1960.
- (253) STASZEWSKI, J. Smoking and cancer of the urinary bladder in males in Poland. *British Journal of Cancer* 20(1): 32-35, March 1966.
- (254) STELL, P.M. Smoking and laryngeal cancer. *Lancet* 1(7751): 617-618, March 18, 1972.
- (255) STELLMAN, J.M., STELLMAN, S.D. *What Proportion of Cancers is Attributable to Occupation? Statistical and Social Considerations*. Paper presented at the American Society for Prevention Oncology, Chicago, March 6-7, 1980.
- (256) STELLMAN, S.D., AUSTIN, H., WYNDER, E.L. Cervix cancer and cigarette smoking: A case-control study. *American Journal of Epidemiology* 111(4): 383-388, April 1980.
- (257) STEVENS, M.H. Synergistic effect of alcohol on epidermoid carcinogenesis in the larynx. *Otolaryngology and Head and Neck Surgery* 87(6): 751-756, November-December 1979.
- (258) STEVENS, R.G., MOOLGAVKOV, S.H. Estimation of relative risk from vital data: Smoking and cancers of the lung and bladder. *Journal of the National Cancer Institute* 63(6): 1351-1357, December 1979.
- (259) STOCKS, P. Cancer incidence in North Wales and Liverpool region in relation to habits and environment. *British Empire Cancer Campaign Annual Report* 35(Supplement to Part II): 66-95, 1957.
- (260) SUSSER, M.W. *Casual Thinking in the Health Sciences. Concepts and Strategies of Epidemiology*. New York, Oxford University Press, 1973.
- (261) SVOBODA, V. An analysis of some possible epidemiological factors involved in carcinoma of the larynx. *Neoplasma* 15(6): 677-684, 1968.
- (262) TAIRA, N., NAKAYAMA, K., HASHIMOTO, K. Nicotinic acetylcholine receptors subserving nociception in the dog hindlimb. *Japanese Journal of Physiology* 20(5): 571-583, October 15, 1970.
- (263) TAKANO, K., OSOGOSHI, K., KAMIMURA, N., KANDA, K., KANE, K., KAMIYAMA, R., SAKAMOTO, K., SATO, H., SHIRAI, Y., SEI, M., TANABE, T., HORINO, M., MINAMI, Y.L., MOTOJI, H.L., MORITA, R., ORIHATA, H.L., HIRAYAMA, T. Schokudogan no ekigaku, toku ni atsui inshokubutsu, inshu, kitsuen narabi, ni eiyo ketsubo ni tsuit [Epidemiology of esophageal cancer—with special reference to the significance of hot food and beverage drinking, smoking, and nutritional deficiency.] *International Journal of Cancer* 5: 152-156, 1970.
- (264) THOMAS, D.B. An epidemiologic study of carcinoma in situ and squamous dysplasia of the uterine cervix. *American Journal of Epidemiology* 98(1): 10-28, July 1973.

- (265) TOKUHATA, G.K. *Cancer of the Lung: Host and Environmental Interaction*. Pennsylvania Department of Health, Harrisburg, Pennsylvania, September 1972, 48 pp.
- (266) TYLECOTE, F.E. Cancer of the lung. *Lancet* 2(4): 256-257, July 30, 1927.
- (267) TYRRELL, A.B., MACAIRT, J.G., McCAUGHEY, W.T.E. Occupational and non-occupational factors associated with vesical neoplasm in Ireland. *Journal of the Irish Medical Association* 64(410): 213-217, April 22, 1971.
- (268) UMIKER, W., STOREY, C. Bronchogenic carcinoma-in-situ. Report of a case with positive biopsy, cytological examination, and lobectomy. *Cancer* 5(2): 369-374, March 1952.
- (269) U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE. *Smoking and Health: A Report of the Surgeon General*. U.S. Department of Health, Education, and Welfare, Public Health Service, Office of the Assistant Secretary for Health, Office on Smoking and Health, DHEW Publication No. (PHS)79-50066, 1979, 1136 pp.
- (270) U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE. *The Health Consequences of Smoking for Women: A Report of the Surgeon General*. U.S. Department of Health, Education, and Welfare, Public Health Service, Office of the Assistant Secretary for Health, Office on Smoking and Health, 1980, 359 pp.
- (271) U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES. *Fourth Special Report to the U.S. Congress on Alcohol and Health*. DeLuca, J.R. (Editor). U.S. Department of Health and Human Services, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute on Alcohol Abuse and Alcoholism, DHHS Publication No. (ADM)81-1080, January 1981, 206 pp.
- (272) U.S. PUBLIC HEALTH SERVICE. *Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service*. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, PHS Publication No. 1103, 1964, 387 pp.
- (273) U.S. PUBLIC HEALTH SERVICE. *The Health Consequences of Smoking. A Public Health Service Review: 1967*. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, DHEW Publication No. 1696, Revised, January 1968, 227 pp.
- (274) U.S. PUBLIC HEALTH SERVICE. *The Health Consequences of Smoking, 1968. Supplement to the 1967 Public Health Service Review*. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, DHEW Publication No. 1696, 1968, 177 pp.
- (275) U.S. PUBLIC HEALTH SERVICE. *The Health Consequences of Smoking, 1969. Supplement to the 1967 Public Health Service Review*. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, DHEW Publication No. 1969-2, 1969, 98 pp.
- (276) U.S. PUBLIC HEALTH SERVICE. *The Health Consequences of Smoking. A Report of the Surgeon General: 1971*. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, DHEW Publication No. (HSM)71-7513, 1971, 458 pp.
- (277) U.S. PUBLIC HEALTH SERVICE. *The Health Consequences of Smoking. A Report of the Surgeon General: 1972*. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, DHEW Publication No. (HSM)72-7516, 1972, 158 pp.

- (278) U.S. PUBLIC HEALTH SERVICE. *The Health Consequences of Smoking. A Report of the Surgeon General: 1973*. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, DHEW Publication No. (HSM)73-8704, 1973, 249 pp.
- (279) U.S. PUBLIC HEALTH SERVICE. *The Health Consequences of Smoking. A Report of the Surgeon General: 1974*. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, DHEW Publication No. (CDC)74-8704, 1974, 124 pp.
- (280) U.S. PUBLIC HEALTH SERVICE. *The Health Consequences of Smoking. A Report of the Surgeon General: 1975*. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, DHEW Publication No. (CDC)76-8704, 1975, 235 pp.
- (281) U.S. PUBLIC HEALTH SERVICE. *The Health Consequences of Smoking. A Reference Edition*. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, DHEW Publication No. (CDC)78-8357, 1976, 657 pp.
- (282) VALKO, P. Koureni a vyskyt zhoubnych novotvaru hrtanu. [Smoking and occurrence of malignant tumors of the larynx.] *Ceskoslovenska Otolaryngologie* 1: 102-105, 1952.
- (283) VINCENT, R.G., MARCHETTA, F. The relationship of the use of tobacco and alcohol to cancer of the oral cavity, pharynx or larynx. *American Journal of Surgery* 106(3): 501-505, September 1963.
- (284) VINCENT, R.G., PICKREN, J.W., LANE, W.L., BROSS, I., TAKITA, H., HOUTEN, L., GUTIERREZ, A.C., RZEPKA, T. The changing histopathology of lung cancer. A Review of 1682 cases. *Cancer* 39(4): 1647-1655, April 1977.
- (285) WAGONER, J.K., ARCHER, V.E., CARROLL, B.E., HOLADAY, D.A., LAWRENCE, P.A. Cancer mortality patterns among U.S. uranium miners and millers, 1950 through 1962. *Journal of the National Cancer Institute* 32(4): 787-801, April 1964.
- (286) WAGONER, J.K., ARCHER, V.E., LUNDIN, F.E., Jr., HOLADAY, D.A., LLOYD, J.W. Radiation as the cause of lung cancer among uranium miners. *New England Journal of Medicine* 273(4): 181-188, July 22, 1965.
- (287) WAGONER, J.K., MILLER, R.W., LUNDIN, F.E., Jr., FRAUMENI, J.F., Jr., HAIJ, M.E. Unusual cancer mortality among a group of underground metal miners. *New England Journal of Medicine* 269(6): 284-289, August 8, 1963.
- (288) WASSINK, W.F. Ontstaansvoorwaarden voor longkanker. [Conditions for the origin of lung cancer.] *Nederlands Tijdschrift voor Geneeskunde* 92(46): 3732-3747, November 13, 1948.
- (289) WATSON, W.L., CONTE, A.J. Smoking and lung cancer. *Cancer* 7(2): 245-249, March 1954.
- (290) WEIR, J.M., DUNN, J.E., Jr. Smoking and mortality: A prospective study. *Cancer* 25(1): 105-112, January 1970.
- (291) WEISS, W. Lung cancer mortality and urban air pollution. *American Journal of Public Health* 68(8): 773-775, August 1978.
- (292) WEISS, W. The cigarette factor in lung cancer due to chloromethyl ethers. *Journal of Occupational Medicine* 22(8): 527-529, August 1980.
- (293) WEISS, W., BOUCOT, K.R., SEIDMAN, H., CARNAHAN, W.J. Risk of lung cancer according to histologic type and cigarette dosage. *Journal of the American Medical Association* 222(7): 799-801, November 13, 1972.
- (294) WEST, D.W. An assessment of cancer risk factors in Latter-day Saints and non-Latter-day Saints in Utah. In: Cairns, J., Lyon, J.L., Skolnick, M. (Editors). *Cancer Incidence in Defined Populations*. Banbury Report No. 4, Cold Spring Harbor, New York, Cold Spring Harbor Laboratory, 1980, pp. 31-49.

- (295) WICKEN, A.J. *Environmental and Personal Factors in Lung Cancer and Bronchitis Mortality in Northern Ireland, 1960-1962*. London, Tobacco Research Council, Research Paper No. 9, 1966, 84 pp.
- (296) WIGLE, D.T., MAO, Y., GRACE, M. Relative importance of smoking as a risk factor for selected cancers. *Canadian Journal of Public Health* 71(4): 269-275, July-August 1980.
- (297) WIGLE, D.T., MAO, Y., GRACE, M. Smoking and cancer of the uterine cervix: Hypothesis. (Letter). *American Journal of Epidemiology* 111(1): 125-127, 1980.
- (298) WILLIAMS, M.J. Extensive carcinoma-in-situ in the bronchial mucosa associated with two invasive bronchogenic carcinomas. Report of case. *Cancer* 5(4): 740-747, July 1952.
- (299) WILLIAMS, R.R., HORM, J.W. Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: Interview study from the Third National Cancer Survey. *Journal of the National Cancer Institute* 58(3): 525-547, March 1977.
- (300) WINKELSTEIN, W., Jr. Reviews and commentary. Smoking and cancer of the uterine cervix. Hypothesis. *American Journal of Epidemiology* 106(4): 257-259, October 1977.
- (301) WINN, D.M., BLOT, W.J., SHY, C.M., PICKLE, L.W., TOLEDO, A., FRAUMENI, J.R., Jr. Snuff dipping and oral cancer among women in the southern United States. *New England Journal of Medicine* 304(13): 745-749, March 26, 1981.
- (302) WOLFF, G., LAUTER, J. Zur Epidemiologie des Magenkrebses. I. Mitteilung. [On epidemiology of gastric cancer. First Communication.] *Archiv für Geschwulstforschung* 46(1): 1-14, 1976.
- (303) WORLD HEALTH ORGANIZATION. *World Health Statistics Annual. Vital Statistics and Causes of Death*. Geneva, World Health Organization, 1977.
- (304) WORLD HEALTH ORGANIZATION. *World Health Statistics Annual. Vital Statistics and Causes of Death*. Geneva, World Health Organization, 1980.
- (305) WRIGHT, N.H., VESSEY, M.P., KENWARD, B., McPHERSON, K., DOLL, R. Neoplasia and dysplasia of the cervix uteri and contraception: A possible protective effect of the diaphragm. *British Journal of Cancer* 38(2): 273-279, August 1978.
- (306) WYNDER, E.L. The epidemiology of cancers of the upper alimentary and upper respiratory tracts. *Laryngoscope* 88(1, Supplement 8, Part 2): 50-51, January 1978.
- (307) WYNDER, E.L., BROSS, I.J. A study of etiological factors in cancer of the esophagus. *Cancer* 14(2): 389-413, March/April 1961.
- (308) WYNDER, E.L., BROSS, I.J., CORNFIELD, J., O'DONNELL, W.E. Lung cancer in women. A study of environmental factors. *New England Journal of Medicine* 255(24): 1111-1121, December 13, 1956.
- (309) WYNDER, E.L., BROSS, I.J., DAY, E. A study of environmental factors in cancer of the larynx. *Cancer* 9(1): 86-110, January-February 1956.
- (310) WYNDER, E.L., BROSS, I.J., FELDMAN, R.M. A study of the etiological factors in cancer of the mouth. *Cancer* 10(6): 1300-1323, November-December 1957.
- (311) WYNDER, E.L., CORNFIELD, J. Cancer of the lung in physicians. *New England Journal of Medicine* 248(11): 441-444, March 12, 1953.
- (312) WYNDER, E.L., COVEY, L.S., MABUCHI, K., MUSHINSKI, M. Environmental factors in cancer of the larynx. A second look. *Cancer* 38(4): 1591-1601, October 1976.
- (313) WYNDER, E.L., GOLDSMITH, R. The epidemiology of bladder cancer. A second look. *Cancer* 40(3): 1246-1268, September 1977.

- (314) WYNDER, E.L., GORI, G.B. Contribution of the environment to cancer incidence: An epidemiological exercise. *Journal of the National Cancer Institute* 58(4): 825-832, April 1977.
- (315) WYNDER, E.L., GRAHAM, E.A. Tobacco smoking as a possible etiologic factor in bronchiogenic carcinoma. A study of six hundred and eighty-four proved cases. *Journal of the American Medical Association* 143(4): 329-336, May 27, 1950.
- (316) WYNDER, E.L., HOFFMANN, D. Tobacco and tobacco smoke. *Seminars in Oncology* 3(1): 5-15, March 1976.
- (317) WYNDER, E.L., HULTBERG, S., JACOBSSON, F., BROSS, I.J. Environmental factors in cancer of the upper alimentary tract. A Swedish study with special reference to Plummer-Vinson (Paterson-Kelly) syndrome. *Cancer* 10(3): 470-487, May/June 1957.
- (318) WYNDER, E.L., KMET, J., DUNGAL, N., SEGI, M. An epidemiological investigation of gastric cancer. *Cancer* 16(11): 1461-1496, November 1963.
- (319) WYNDER, E.L., MABUCHI, K., BEATTIE, E.J., Jr. The epidemiology of lung cancer. Recent trends. *Journal of the American Medical Association* 213(13): 2221-2228, September 28, 1970.
- (320) WYNDER, E.L., MABUCHI, K., MARUCHI, N., FORTNER, J.G. A case control study of cancer of the pancreas. *Cancer* 31(3): 641-648, March 1973.
- (321) WYNDER, E.L., MABUCHI, K., MARUCHI, N., FORTNER, J.G. Epidemiology of cancer of the pancreas. *Journal of the National Cancer Institute* 50(3): 645-667, March 1973.
- (322) WYNDER, E.L., MABUCHI, K., WHITMORE, W.F., Jr. Epidemiology of adenocarcinoma of the kidney. *Journal of the National Cancer Institute* 53(6): 1619-1634, December 1974.
- (323) WYNDER, E.L., MUSHINSKI, M.H., SPIVAK, J.C. Tobacco and alcohol consumption in relation to the development of multiple primary cancers. *Cancer* 40(4): 1872-1878, October 1977.
- (324) WYNDER, E.L., NAVARRETE, A., AROSTEGUI, G.E., LLAMBES, J.L. Study of environmental factors in cancer of the respiratory tract in Cuba. *Journal of the National Cancer Institute* 20(4): 665-673, April 1958.
- (325) WYNDER, E.L., ONDERDONK, J., MANTEL, N. An epidemiological investigation of cancer of the bladder. *Cancer* 16(11): 1388-1407, November 1963.
- (326) WYNDER, E.L., STELLMAN, S.D. Comparative epidemiology of tobacco-related cancers. *Cancer Research* 37(12): 4608-4622, December 1977.
- (327) WYNDER, E.L., STELLMAN, S.D. Impact of long-term filter cigarette usage on lung and larynx cancer risk. A case-control study. *Journal of National Cancer Institute* 62(3): 471-477, March 1979.
- (328) WYNDER, E.L., WRIGHT, G. A study of tobacco carcinogenesis. I. The primary fractions. *Cancer* 10(2): 255-271, March/April 1957.
- (329) YESNER, R. Histologic typing of lung cancer with clinical implications. *Frontiers of Radiation Therapy and Oncology* 9: 140-150, 1974.
- (330) YOSHIDA, O., MIYAKAWA, M., HARADA, T., OKADA, K. Bokogan no ekigaku ni okeru mondaiten. [Problem points in epidemiology of bladder cancer.] *Nihon Rinsho* 26(8): 1850-1854, August 1968.

PART III. MECHANISMS OF CARCINOGENESIS

METHODOLOGY OF EXPERIMENTAL CHEMICAL CARCINOGENESIS

Experimental Assessment of Carcinogenicity

In order to determine the possible carcinogenicity of tobacco smoke constituents, the same procedures should be employed as are used for other substances. Various criteria and guidelines for carcinogenicity tests have been advocated by several governmental and international agencies and by various advisory groups. For example, the World Health Organization (WHO) (29), the International Agency for Research on Cancer (IARC) (8), the Environmental Protection Agency (3), the Food and Drug Administration (4), the National Cancer Institute - National Toxicology Program (22), Health and Welfare of Canada (2), and the Health Council of the Netherlands (13), as well as others, have issued guidelines for the testing of compounds for different aspects of acute and chronic toxicity.

Chemicals

As a first step in the testing of any material for possible carcinogenicity, the researcher should obtain a complete physico-chemical characterization of the material. Examinations by such techniques as thin-layer, gas-liquid, or high performance liquid chromatography should afford some idea of whether the material is homogeneous or a mixture of components. If the last is the case, identification of the individual components and determination of the level of each in the mixture are highly desirable. Otherwise, the validity and significance of the results may be questioned.

Factors Influencing Carcinogenicity

In tests for possible carcinogenicity, several factors influence the outcome of any study. Those relevant to the compound are the route of administration and the dose and frequency of administration. Factors relating to the animal are the species, strain, sex, age, diet, spontaneous tumor incidence, and immunological status.

Route of Administration

Oral administration

In addition to being a logical technique for testing compounds that may be ingested by humans, oral administration is also useful for compounds that may be inhaled as dusts, cleared from the airways by ciliary action, and then swallowed. Compounds may be mixed in the feed, given as aqueous solutions instead of normal drinking water, given by gavage at appropriate intervals, or even given in capsules. If the compound is mixed with the feed, the uniformity of

mixing, the stability in the diet, and the nonreactivity with the feed are factors of concern. Volatile compounds should not be given in the diet, for the resultant loss will lead to inaccuracies in dose levels. If given in the drinking water, solubility and stability must be considered.

Dermal

The dermal route simulates exposure of the skin as it occurs in occupational situations or in the use of cosmetics, and has been used as a standardized carcinogenicity assay. Application of a solution of the test material by means of a pipet should be made in an area that cannot be reached by the animal. Otherwise, the animal will lick the treated area so that oral ingestion occurs. To avoid the animals' licking each other, single caging is desirable. In this type of test, mice, hamsters, rabbits, and sometimes rats are used. For cutaneous application, mice of the BALB/c, C3Hf, or DBA strains or the non-inbred Swiss strain are most responsive. SENCAR mice have been especially bred for sensitivity in initiation-promotion assays. The skin should be clipped before application of the test compound, but abrasion or mechanical injury of the skin should be avoided.

Implantation: Subcutaneous and Intramuscular

Although subcutaneous injection of polycyclic aromatic hydrocarbons in mice has proved to be quite reliable as a test system, the use of this test in other species has led to controversial results. The induction of tumors at the implantation site, especially in rats, by inert materials of the proper size, by saline solutions, or by oily solvents has indicated the limitation of this test.

Injection: Intraperitoneal and Intravenous

Intraperitoneal and intravenous injections may be used to test drugs, but for various reasons are not suitable for repeated dosing. They are useful for administering a single dose or a few doses of potent carcinogens for model experiments. With this technique, exposure of personnel to carcinogens is minimized.

Inhalation

Inhalation is the major route by which persons are exposed to cigarette smoke. For laboratory study, complex installations, such as pumps or metering devices, are needed to allow uniform delivery of the test material to the experimental animals. Scrubbers and other devices are required to prevent exposure of any personnel working in the area. A test by the inhalation route usually costs much more than studies using other routes of administration.

In lieu of using large inhalation chambers in which animals are exposed, it is possible to use chambers into which the head and nose of individual animals are fitted. The test material is then forced into the chamber, resulting in an inhalation exposure. Relatively few animals can be treated with a given chamber by this method, however.

Factors that should be considered in evaluating the results of the test are effects on secretion of mucous, alteration of pulmonary ventilation, and possible toxicity to the cilia in the respiratory tract.

The dilemma is that in rodents the anatomy and physiology of the respiratory tract and the biochemistry of the lung differ from that of humans and that animals anatomically resembling the human most closely are too expensive and have lifespans too long to permit their use in routine tests.

For inhalation tests of the carcinogenicity of tobacco smoke and various fractions of tobacco smoke, hamsters are preferable to rats and mice because they respond with a higher incidence of airway tumors (6).

Higher dose levels, greater frequency of administration, and longer periods of observation are required for weak carcinogens than are needed for potent ones. For example, potent carcinogens such as 7,12-dimethylbenz[a]anthracene or nitrosomethylurea can induce cancers in certain animals after a single dose. On the other hand, a single or very low dose of compounds such as N-2-fluorenylacetamide, safrole, and dioxane may not lead to tumors within the lifespan of the animal.

Animal Factors

Species

The choice of species rests on several factors, including lifespan, size, sensitivity to a specific class of compound, and availability. Early studies on skin painting of benzo[a]pyrene showed that mice and rabbits were responsive, while the few other species tested were less responsive. Guinea pigs are not suitable for testing aromatic amides and amines or their precursors. They either lack the enzyme system that activates aromatic amines or degrade the activated metabolite so rapidly that there is no effect. Overall, mice are the most useful animals for skin painting bioassays; rats are useful for test material that might be fed, especially with nitroso compounds or aromatic amines; and hamsters seem better suited for inhalation studies on tobacco smoke or its components.

Larger species including the rabbit, dog, and primate require a longer time to obtain results; they are expensive to purchase, to maintain, and to test; and they are not always readily available.